IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 040283-0182

re patent application of
David Reginald ADAMS et al.
Serial No. 09/600,631
Filed: February 12th, 2001

Group Art Unit: 1626
Examiner: R. Anderson

For: AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

DECLARATION UNDER 37 CFR § 1.132 OF NATHANIEL JULIUS MONCK

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Nathaniel Julius Monck, the undersigned, a citizen of Great Britain and a resident of Wokingham, United Kingdom, do hereby declare that:

1. I am one of the co-inventors of the invention described in the above-identified patent application entitled "AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS" which was given United States Serial No. 09/600,631, and accordingly I am familiar with the content of the present application.

2. I graduated as a Bachelor of Science from University of Bristol in 1990, and completed a Doctoral Degree from Imperial College, London University in 1993.

3. Since August 1996, I have been employed by VERNALIS RESEARCH LIMITED, assignee of the above-identified application, where I have been engaged in research and development of drugs useful in the treatment of CNS disorders, particularly anxiolytics.

4. I attach my Curriculum Vitae.

5. It is my understanding that the Examiner considers that the (amended) claims of this Application are not distinct over GB-872447 on the basis that the term "substituted aryl" could cover "aryl substituted by hydrogen". I consider that the Examiner's interpretation of this nomenclature is not correct and is opposite to that of the person skilled

in the art. The skilled person would use the term "unsubstituted aryl" to refer to an aryl ring wherein all atoms bound to the ring atoms are hydrogen, whereas the term "substituted aryl" would be used to refer to an aryl ring wherein one or more of the hydrogen atoms has been replaced by some other group. Accordingly, the term "substituted aryl" would not be understood by the skilled person to cover "aryl substituted by hydrogen".

6. In addition, the Examiner states that the "the broadest reasonable interpretation" of claim 1 would include the compounds of GB-872447. I consider that the Examiner's interpretation is not a "reasonable" one. If the term "substituted aryl" refers to aryl groups wherein the atoms bound to the ring atoms include hydrogen as well as halogen, haloalkyl etc., then one must consider what the term "unsubstituted aryl" refers to. Using the Examiner's logic, there would be no atom bound to the ring atom, thereby creating a highly unstable radical, which is an unreasonable result. The skilled person would not use the term "unsubstituted aryl" to refer to such a radical.

7. In summary, because the claims of this Application require that R^1 is "substituted aryl", I consider that the claimed subject-matter is novel over GB-872447 which only discloses compounds wherein the corresponding aryl group is unsubstituted (i.e. the aryl group has hydrogen atoms bound to the ring carbon atoms).

8. It is my understanding that the Examiner also considers that the claimed subject-matter is obvious over GB-872447 and EP-0194112. In order to establish the patentability of the present invention, experiments were carried out by me or under my direct supervision to provide additional experimental data to prove that the compounds claimed in the present Application are unexpectedly superior over those of this prior art. The experimental results are presented in Table 1 below.

Table 1

Compound	Dose (mg/kg s.c.)	ED_{50} (Confidence limits)
Vehicle	-	18.5 (17.2-19.9)
Example 20	15	25.5 (22.8-27.4)*
Example 20	30	28.5 (26.4-30.6)*
1-carbamoyl-3-phenylazetidine	15	22.1 (19.0-25.6)
1-carbamoyl-3-phenylazetidine	30	22.9 (-)*

* = Significant Effect

9. The results show that the minimum effective dose of Example 20 to block 3-MPA-induced seizures is less than or equal to 15 mg/kg, whereas the minimum effective dose for 1-carbamoyl-3-phenylazetidine is 30 mg/kg. Thus, the compound of Example 20, which contains a substituted aryl group, is an unexpectedly more potent anti-convulsant agent than the prior art compound which contains an unsubstituted aryl group. I consider that this improvement could not have been predicted, whether in view of GB-872447 or a combination of GB-872447 and EP-0194112.

10. I note that in the Office Action dated 19th September 2002, the Examiner states that:

> *"... the Comparative experiments on pages 4 and 5 [of the last response] ... lack a showing of unexpected results since the results overlap in range due to confidence limits."*

It is agreed that the result for Example 20 overlaps with that of the prior art compound when the confidence limits for the ED_{50} values are taken into consideration. However, this does not mean that the results are not significant. The results show that Example 20 and the prior art compound are not significantly different relative to each other since the confidence limits overlap, but this was not what the experiments were designed to test. At 15 mg, Example 20 is significantly different from the vehicle and therefore active, whereas the prior art compound is not significantly different and therefore not active. It is therefore entirely valid to conclude that Example 20 is more potent than the prior art compound. I consider that this

increased potency could not have been predicted from the prior art, and therefore that the presently claimed subject-matter is not obvious.

I further declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2nd January 2002

Nathaniel Julius Monck

Nathaniel Julius Thomas Monck

10 Park Crescent, Sunningdale, Berkshire, SL5 0AX, UK.

Date of Birth: 16 July 1968

Professional Experience:

Aug 1996-present date	**Vernalis Research Ltd**, Winnersh Triangle. Principal Scientist, Chemistry Dept. Anxiety Project Leader (chemistry) 1997-2001 Sodium Channel Project Leader (chemistry) 2001-present date
Feb 1996-Aug 1996	**SmithKline Beecham**, Harlow. Industrial post-doctoral position. Synthesis of conformationally restricted unnatural amino-acids and incorporation into peptide mimetic libraries via combinatorial chemistry.
Feb 1995-Nov 1995	**The Australian National University**, Canberra, ACT. Post-Doctoral Research Fellow Research Advisor: Professor Lewis N. Mander, FRS Studies towards the total synthesis of gibberellic acid GA_{103}, the total synthesis of Harringtonolide and the partial synthesis of 7β-hydroxy-kaur-16-en-19-oic acid.
Jan 1994-Jan 1995	**The Ohio State University**, Columbus, Ohio. Post-Doctoral Research Fellow Research Advisor: Professor Leo A. Paquette Studies towards the total synthesis of Jatrophatrione.
Oct 1990-Dec 1993	**Imperial College**, University of London. Research Fellow; Research Advisor: Professor Steven V. Ley, FRS Development of new synthetic methods for the total synthesis of Milbemycin α_1 and Nemadectin β utilising relay studies of Nemadectin γ. Undergraduate Teaching Assistant; supervision and demonstration of laboratory experiments.
Oct 1992-Dec 1992	**Rhône-Poulenc-Rorer**, Dagenham. Research Fellow; Research Advisor: Dr Michael Ashton CASE award industrial placement.
Jul 1989-Aug 1989	**Institute of Child Health/Great Ormond Street Hospital**, London. Research Assistant; Research Advisor: P. Bird. Studies towards the development of HPLC methods for the analysis of samples from neofibroblastomer patients.

Awards/Honours:

1997-1998	MRSC CChem awarded as result of Structured Assessment.
1990-1993	CASE Award from Rhône-Poulenc-Rorer.

Courses:

Dec 1998	Introduction to Molecular Modelling, including the use of Legion, Selector, Flexidock and Gasp operations; Tripos Inc., Milton Keynes
July 1997	Medicinal Chemistry Residential Course: An introduction to the pharmaceutical industry. RSC, Canterbury.

Education:

1990-1993	Imperial College, University of London PhD, DIC, Synthetic Organic Chemistry Research Advisor: Professor Steven V. Ley, FRS Dissertation: Studies towards the Total Synthesis of the Milbemycins.
1987-1990	University of Bristol, Bachelor of Science (Hons), Chemistry, First class. Final year project supervisor: Dr Thomas V. Lee Dissertation: The Use of Enzymes in Organic Media.
1979-1986	Acland Burghley Comprehensive School, London A-levels: Chemistry (A), Mathematics (B), Physics (A) O-levels: French, History, Geography, Music, Chemistry, Physics, Mathematics, Advanced Mathematics, English Literature, English Language.

Bibliographic Information

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Preparation of azetidine carboxamides for the treatment of CNS disorders. Snape, Mike Frederick; Fletcher, Allan; Stanhope, Kelly Jean; Monck, Nathaniel Julius. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 39 pp. CODEN: PIXXD2 WO 0107043 A1 20010201.

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2-adamantanemethanamine compounds for treating abnormalities in glutamatergic neurotransmission, and preparation thereof. Gillespie, Roger John; Monck, Nathaniel Julius Thomas; Bird, Andrew James; Ward, Simon Edward. (Vernalis Research Limited, UK). PCT Int. Appl. (2000), 35 pp. CODEN: PIXXD2 WO 0044371 A1 20000803.

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